IRB EFFICACY REVIEW

PRODUCT NAMES:	CONTRAC ALL-WEATHER BLOX
PRODUCT NO.:	12455-79
REGISTRANT:	Bell Laboratories, Inc. Madison, WI 53704
DATE COMPLETED:	4/29/15
DP NUMBERS:	426487
DECISION NUMBERS:	500025
GLP CLAIMED:	Yes
DATES OF SUBMISSION:	2/3/15 (received 2/3/15, sent for review 3/31/15)
ACTIVE INGREDIENT:	Bromadiolone
FORMULATION:	0.005% a.i. bait blocks
TYPE OF PRODUCT:	Rodenticide
PURPOSE:	Application to add new targeted species claims
DATA MRID NUMBERS:	495528-01 (deer mice, laboratory study) 495528-02 (deer mice, laboratory study)
TEAM REVIEWER:	Gene Benbow, M.S.
EFFICACY REVIEWER:	William W. Jacobs, Ph. D. 4/29/15
SECONDARY REVIEWER:	Gene Benbow, M.S. 4/29/15

BACKGROUND

EPA Reg. No. 12455-79 is a 0.005% Bromadiolone 1-oz bait block currently registered such that, according to its "**Pest Control Operator Use Label**", it

> can only be used to control Norway rats, roof rats, and house mice in and within 100 feet of man-made structures constructed in a manner so as to be vulnerable to commensal rodent invasions and/or to harboring and attracting rodent infestations. Examples of such structures include homes and other permanent or temporary residences, food processing facilities, industrial and commercial buildings, trash receptacles, agricultural and public buildings, transport vehicles (ships, trains, aircraft), docks and port of [sic] terminal buildings and related structures around and associated with these sites. Fence and perimeter baiting beyond 100 feet from a structure, as defined above, is prohibited. This product must not be applied directly to food or feed crops.

According to its "**AGRICULTURAL USE LABEL**", this same product

> can only be used to control Norway rats, roof rats, and house mice in and within 100 feet of man-made agricultural buildings and man-made agricultural structures constructed in a manner so as to be vulnerable to commensal rodent invasions and/or to harboring and attracting rodent

infestations. Fence and perimeter baiting beyond 100 feet from an agricultural structure, as defined above, is prohibited. This product must not be applied directly to food or feed crops.

See efficacy reviews of 3/26/92, 7/23/92, 12/31/92, 9/8/94, 7/25/95, 9/5/96, 12/29/97, 4/16/98, 9/3/02, 7/18/03, and 9/24/04, along with other relevant items in the registration jacket. This product was registered on 4/14/92 and reregistered on 3/18/2009. Its current label was "ACCEPTED" on 4/13/12.

This review assesses an amendment application via which Bell seeks to add claims for controlling 9 new categories of targeted pests to the label for this product. The package routed for efficacy review includes copies of the following documents: the amendment application form (8570-1) dated "February 3, 2015" and attributed to John Lublinkhof, Bell's "Director of Regulatory Affairs"; a letter of application dated "February 3, 2015, and signed by Lublinkhof; a one-page data "**TRANSMITTAL DOCUMENT**" (MRID# 495528-00), signed by Lublinkhof and dated "February 6, 2015"; a completed "Certification with Respect to Citation of Data" form, signed by Lublinkhof and dated "02/03/15"; a three-page "**DATA MATRIX**" document dated "Feb 3, 2015" and signed by Lublinkhof; a copy of a proposed revised label; a copy of the product's basic Confidential Statement of Formula (CSF), dated "10/24/2013"; and an OPP "**BEAN SHEET**" document dated "**31-Mar-2015**". I subsequently obtained one copy each of two efficacy data reports. The efficacy reports are cited and discussed later in this review. The efficacy reports and the documents dated for February of 2015 were part of an "E-SUBMISSION".

During the course of this review, I requested from Lublinkhof documentation regarding the composition of baits and challenge diets used in the efficacy trials. The documents that he subsequently provided are identified and discussed (below) in the sections of this review where the information is most relevant.

In his 2/3/15 letter, Lublinkhof cites to "the EPA/APSCRO agreement" as the basis for Bell's application to add to this product's label claims for controlling

> the following rodents: Cotton mouse, Cotton rat, Deer mouse, Eastern harvest mouse, Golden mouse, Pack rat, Polynesian rat, Meadow vole, and White footed mouse.

The "agreement" is in the form of a letter of January 21, 2015, from Meredith F. Laws, Chief of the Invertebrate and Vertebrate Branch 3, to John W. Scott, President of the Association of Structural Pest Control Regulatory Officials (APSCRO). Among other things, the letter of 1/21/15 states that

> Registrants may submit applications to amend their labels to remove the 2ee restriction imposed by EPA and include the following text proposed by APSCRO:
>
> > "This product may only be used to control the following rodent pests in and around man-made structures:
> >
> > House mouse (Mus musculus)
> > Norway rat (Rattus norvegicus)
> > Roof rat (Rattus rattus)
> > Cotton mouse (Peromyscus gossypinus)
> > Cotton rats (Sigmodon spp.)
> > Deer Mouse (Peromyscus maniculatus)
> > Eastern harvest mouse (Reithrodontomys humulis)
> > Golden mouse (Ochrotomys nuttalli)
> > Pack rats (Neotoma spp.)
> > Polynesian rats (Rattus exulans)
> > Meadow vole (Microtus pennsylvanicus)
> > White footed mouse (Peromyscus leucopus)"

The referenced proposal from APSCRO came in the form of a September 24, 2014, letter from Scott to Laws.

Bell Laboratories, Inc., is one of several registrants of commensal rodenticide bait products to submit amendment applications to add to the labels of such products claims for controlling the types of rodents listed in the APSCRO letter that were not already being claimed on those labels.

Regarding such anticipated amendment applications, the Laws letter of 1/21/15 included the text quoted below.

> It is important to note that EPA will evaluate the amendments individually, and at our discretion supporting laboratory data may be required. Additionally, this revision cannot be applied to field-use rodenticide products.

Peromyscus spp. rodents, and especially the deer mouse (*P. maniculatus*) and the white-footed mouse (*P. leucopus*), currently are the most important nonhuman vertebrate vectors of diseases of public health significance in the U.S.[1] The cotton mouse (*P. gossypinus*) and the oldfield mouse (*P. polionotus*) essentially are the ecological replacements for deer mice and white-footed mice in the southeastern U.S., where the cotton mouse also seems to replace them as vectors. Consequently, EPA has decided to require efficacy data to support claims for adding any of these *Peromyscus* species to labels of rodenticide baits that are to be used in commensal situations. Likely due to their not being mentioned in the Laws letter of 1/21/15, no registrant has requested addition of label claims for controlling oldfield mice.

The efficacy data reports included with Bell's amendment application of 2/3/15 for this product pertain to laboratory efficacy trials involving deer mice.

DATA SUMMARY

Formulations

The basic CSF dated 10/24/13 seems to be the only CSF that is current for this product. See the "CONFIDENTIAL ATTACHMENT" to this review for further relevant discussions.

Efficacy Data – Deer Mice

The efficacy reports included in the efficacy review package pertain to laboratory choice-feeding trials. These items are cited and discussed individually below.

Jeans, S.N. (1999) Efficacy of Bromadiolone All-Weather Blox on young adult *Peromyscus maniculatus*. Unpublished report, study no. BEL/0999/BE430, Bell Laboratories, Inc., Madison, WI, 91 pp.

MRID# 495528-01

This study reportedly was patterned after "EPA Test Method 1.214" and run consistently with "EPA Good Laboratory Practices, 40 CFR Part 160". Specifically, Jeans reports having followed "SOP B114 (02/23/93" and "Protocol Number: BEL/0999/BE430". Protocol 1.214 is a method developed by EPA for screening anticoagulant bait-block products for efficacy against house mice under laboratory conditions. Protocol 1.216 is the method that EPA developed for testing anticoagulant baits with *Peromyscus* spp. That method pertains to "dry bait rodenticide products", which could be construed as including bait blocks, although for testing bait blocks with commensal rodents EPA developed protocols that have identification numbers distinct from those used for testing "dry" baits. Aside from their being used for different types of mice, the most relevant procedural difference between Protocols 1.214 and 1.216 is that they call for use of different challenge diets. As elaborated further below, Jeans addressed that difference by using the challenge diet prescribed in Protocol 1.216 in her adaptation of Protocol 1.214 for this study. Jeans (1999) did not attach copies of any of the protocols mentioned in the report but did provide tabular listings of 61 Standard Operating Procedures (SOP) references. Of those SOPs, 28 were checked as having been relevant to this study.

---

[1] These species vector Lyme disease and hanta virus pulmonary syndrome among other maladies.

Jeans (1999) refers to the test material as "Bromadiolone All-Weather Blox" and describes it as "Blue wax blocks" from "batch number: 03241". Jeans reports that the test material was assayed on 8/18/99 and found to be "0.00596% bromadiolone" and that it was assayed again on 10/4/99 and found to be "0.00581% bromadiolone". "CERTIFICATE OF ANALYSIS" sheets appended to the Jeans (1999) report indicate that "LOT# 03241", consisting of "BLUE BLOCKS", was assayed on 8/18/99 and on 10/4/99 with results matching the figures indicated in the narrative portion of the Jeans (1999) report. The assay dates were 1 and 48 days after the reported date of bait manufacture, 8/17/99.

Bell's submission of 2/3/15 lacked batch sheets to document the composition of the test material. At my request, Lublinkhof provided batch sheets for preparations relevant to this efficacy study and the one (Jeans, 2000) that is discussed later in this review. The first of those items were submitted on 4/9/15.

See the CONFIDENTIAL ATTACHMENT to this review for a comparison of the assay results reported for the test material to the certified limits for Bromadiolone shown on the current and then-current CSFs for 12455-79. As noted in the CONFIDENTIAL ATTACHMENT, the composition of batch "03241" corresponded sufficiently well to the CSF dated 10/24/13 for 12455-79 to allow this efficacy trial to be used to support claims for controlling deer mice with the product's current formulation.

Another "CERTIFICATE OF ANALYSIS" appended to the Jeans (1999) report indicates that batch "EF-001" of "EPA FIELD DIET", described as "BROWN MEAL") used in this trial was assayed on 8/24/99 and found to be free of detectable Bromadiolone contamination ("Limit of Detection = 0.145", or 0.0000145%). Jeans provides essentially no information regarding the composition of the challenge diet but does list Bell's standard operating procedure (SOP) "BIO020.1" on "FORMULATION OF FIELD RODENT CHALLENGE DIET" among the SOPs relevant to this trial. That SOP is dated "08/16/99" and, thus was created or revised on the day before the manufacture date of the toxic bait and 8 days before the assay date of the challenge diet used in this bioassay.

At my request, Lublinkhof provided (on 4/9/15) copies of "**SOP NO.:** BIO020.1" and batch sheets for the lots of challenge diet that were used in the Jeans (1999) and Jeans (2000) efficacy studies. The SOP describes procedures for preparing batches of field rodent challenge diet that would be in compliance with the specifications in Protocol 1.216 (50% ground steam-rolled whole oats and 50% ground laboratory rodent diet, with particle-size specifications for each component). The formulation sheet for "**BATCH NO.** *EF-001* ", containing "**COMMERCIAL RODENT LABORATORY DIET**" from "**LOT#:** *062999 MA* ", in addition to "**STEAM ROLLED OATS**" obtained on "*8/17/99*", is consistent with preparation on 8/17/99 of a 5.405-kg amount of field rodent diet conforming to the relevant specifications in Protocol 1.216.

For the bioassay, a test group of 20 young adult deer mice (10 males, 10 females) and a similarly comprised control group were established. The mice were obtained on 8/25/99 from the Peromyscus Stock Center, University of South Carolina, Columbia, SC, and were reported to have been about 8-10 weeks old "at study initiation." The mice were housed in single-sex subgroups of 5 animals each "in suspended stainless steel caging." Cage dimensions reportedly were "16.0"L x 10"W x 7"H" which would have made them 160 in^2 (1032 cm^2) in bottom area, or just over half of the 2.15 ft^2 (2000 cm^2) minimum size indicated in Protocols 1.214 and 1.216 when house mice and *Peromyscus* spp., respectively, are group-caged. Prior to the start of the bait-exposure phase of the trial, the mice were kept under these conditions for a 3-day acclimation period, during which time, according to Protocol 1.216, they should have been fed a commercial diet formulated for feeding mice.

Males in the test group weighed 15.8-22.1 g (mean = 19.2 g) 3 days before the bait-exposure phase of the bioassay began. At the same time, test-group females averaged 18.7 g (range = 16.6-20.1 g); control-group males averaged 17.9 g (range = 16.5-20.0 g); and control-group females averaged 17.5 g (range = 14.1-21.0 g). The differences in mean weights between the sexes were 0.5 g in the test group and 0.4 g in the control group. Those figures are well below the 5-g maximum difference in mean weight between sexes that is stipulated in Protocol 1.216.

Test-group mice were to be offered a choice between the test bait and "EPA Field Rodent Challenge Diet for a 15-day period (9/13-28/99), after which time any surviving mice were to be maintained on challenge diet and observed for 5 more days or until they died, if sooner. Control-group mice were to be maintained on challenge diet for 20 straight days (9/13-10/3/99).

The diets reportedly were offered in "jars". At the start of the bait-exposure period (9/13/99), 4 jars were placed, one per corner, in each cage. One jar at either end of the container contained the toxic bait, and the other contained challenge diet. Positions of the jars were alternated daily, following weigh-backs to assess amounts of diets removed, but with each end of the cage always having one jar containing bait and another containing challenge diet. This feeding arrangement was maintained for 15 consecutive days for the test group, after which time any survivors were monitored for 5 additional days and fed only challenge diet in 2 jars per cage. Control-group mice received 4 jars of challenge diet only for 15 days, with daily container rotations, followed by 5 days with 2 containers of challenge diet per cage.

Results of this bioassay are summarized in Table 1. Test-group mortality was 95%, exceeding the criterion of 90% for Protocol 1.216. Test-group victims died 3-14 days from the onset of bait exposure. The survivor was a female.

All 10 test-group males lost weight (1.0-4.2 g) from 3 days prior to the start of the bait-exposure acclimation period until they expired. Eight of the 9 test-group female victims reportedly lost weight (0.9-4.0 g) by the times that they died, while one gained 1.7 g. The survivor lost 1.7 g. Toxic symptoms reported for test-group animals included rough hair coat, prone position, lethargy, catalepsy, lacrimation, and ataxia. The survivor exhibited symptoms of rough hair coat for 5 days (9/24-28/1999) and was ataxic on one day. By the last 2 days of the post-exposure monitoring period, that animal was back to being described as "*Normal*". The symptoms reported for test-group subjects are not inconsistent with anticoagulant poisoning. Necropsies were not reported.

All control-group subjects survived the 20 days from the start of the acclimation period to the end of the 5-day post-exposure monitoring period. Over that course of time, 3 control-group males gained weight (0.2-1.1 g), 6 lost weight (0.4-2.7 g), and one maintained its initial weight. Four control-females gained weight (0.5-1.2 g), four lost weight (0.4-2.4 g), and 2 maintained their initial weights. All control-group mice were rated as "*Normal*" throughout the acclimation period and the subsequent 20 days.

Composite bait acceptance by the test-group was 37.7% (Table 1). Composite acceptance by females was similar to that by males, although male cage #1 had the lowest composite acceptance of any subgroup and was the only subgroup in which composite acceptance was below the 33% criterion indicated in Protocol 1.216. The female survivor was the only mouse alive in female cage #1 for the last 6 days of the bait-exposure period, during which time 4.1 g of toxic bait consumption and 11.0 g of challenge diet consumption were recorded (29.1% acceptance).[2]

Control-group mice were calculated to have consumed 773.1 g of challenge diet during the 15-day bait-exposure phase of this trial and an additional 281.0 g during the 5-day post-exposure monitoring period for a grand total of 1054.1 g. As 20 mice were in that group for 20 days (i.e., 400 mouse-days), mean daily consumption per "*Normal*" individual works out to 2.6 g/mouse/day.

Jeans (1999) reports that test-room temperatures were 19-26°C (~66-79°F) during the bioassay. That range in temperatures went beyond the range of 20-25°C (68-77°F) that is specified in Protocol 1.216. Relative humidity in the test room reportedly was 43-78% and, therefore, strayed well beyond the range of 50-55% that is stipulated in Protocol 1.216. Without citing evidence regarding the effects of temperature or relative humidity on the performance of anticoagulant rodenticides, Jeans states that "these deviations should not affect the integrity of the study."

---

[2] If this mouse did ingest 4.1 g of a 0.005% Bromadiolone bait over those 6 days, its cumulative dosage, based upon its initial weight of 19.2g and assuming no prior bait consumption, would have been 19.7 mg/kg of body weight. From Table 1, it is clear that the 5 mice in male cage #1 averaged less bait consumption than 4.1 g and all succumbed.

In a "**STUDY DIRECTOR LABORATORY COMMUNICATION**" note dated "*10-4-99*", Jeans acknowledges that temperature and relative humidity went "beyond the protocol's specified range" but declares that "These deviations should not affect study integrity." Jeans would not have been in a position to know if such actually was the case (e.g., whether temperature or humidity fluctuations affected the viability of any deer mice that ate relatively little bait). Low humidity could potentiate the effects of an anticoagulant and likely would increase consumption of water. However, the deviations from the required ranges of temperature and humidity were not extreme on the low ends; and the amounts of bait reportedly ingested by test sub-groups likely were sufficient to have killed the mice in them without assistance from fluctuations in temperature or humidity. Still, Bell's facility should be upgraded so that there is better control over temperature and relative humidity.

Except for the problems with controlling temperature and relative humidity in the test facility and the use of cages that were only about half the size specified in Protocol 1.216 if deer mice are group-caged, this efficacy trial appears to have been conducted competently. Results in the test group exceeded the criteria in Protocol 1.216 for bait acceptance (33%) and mortality (90%). The study is accepted with reservations.

Jeans, S.N. (2000) Efficacy of Bromadiolone All-Weather Blox on young adult *Peromyscus maniculatus*. Unpublished report, study no. BEL/0500/BE462, Bell Laboratories, Inc., Madison, WI, 89 pp.

MRID# 495528-02

This study reportedly was patterned after "EPA Test Method 1.214 (12/02/90) and EPA Test Method 1.216 (07/04/91)" and run consistently with "EPA Good Laboratory Practices, 40 CFR Part 160". Specifically, Jeans reports having followed "SOP BIO509.1 (05/12/00" and "Protocol Number: BEL/0500/BE462". As noted above for the Jeans (1999) report, Protocol 1.214 is a method used to screen anticoagulant bait-block products for efficacy against house mice under laboratory conditions; and Protocol 1.216 is the method that EPA developed for testing anticoagulant baits with *Peromyscus* spp. In essence, the Jeans (2000) study seems to be a replication of the Jeans (1999) study.

Jeans (2000) did not attach copies of any of the protocols mentioned in the report but did provide tabular listings of 56 Standard Operating Procedures (SOP) references. Of those SOPs, 25 were checked as having been relevant to this study.

Jeans (2000) refers to the test material as "Bromadiolone All-Weather Blox" and describes it as "Blue wax blocks" from "batch number: 68061". Jeans reports that the test material was assayed on 5/8/00 and found to be "0.00540% bromadiolone" and that it was assayed again on 6/7/00 and found to be "0.00546% bromadiolone". "CERTIFICATE OF ANALYSIS" sheets appended to the Jeans (2000) report indicate that "BATCH# 68061", consisting of "BLUE BLOCKS" was assayed on 5/8/00 and on 6/7/00 with results matching the figures indicated in the narrative portion of the Jeans (2000) report. The assay dates were 4 and 34 days after the reported date of bait manufacture, 5/4/00.

Although Bell's submission of 2/3/15 lacked batch sheets to document the composition of the test material, Lublinkhof provided them on 4/9/15.

See the CONFIDENTIAL ATTACHMENT to this review for a comparison of the assay results reported for the test material to the certified limits for Bromadiolone shown on the current and then-current CSFs for 12455-79. The composition of batch "68061" corresponded sufficiently well to the CSF dated 10/24/13 for 12455-79 to allow this efficacy trial to be considered to be relevant to this product, but revisions to that CSF are needed. See the CONFIDENTIAL ATTACHMENT.

Another "CERTIFICATE OF ANALYSIS" appended to the Jeans (2000) report indicates that batch "EF-005" of "EPA FIELD DIET", described as "BROWN MEAL") used in this trial was assayed on 5/15/00 and found to be free of detectable Bromadiolone contamination ("Limit of Detection = 0.145", or 0.0000145%). Jeans (2000) provides essentially no information regarding the composition of the challenge diet, but

Lublinkhof subsequently (4/9/15) supplied a copy of Bell's standard operating procedure (SOP) "BIO020.1" on "FORMULATION OF FIELD RODENT CHALLENGE DIET", which Jeans had cited as being among the SOPs relevant to this trial. See discussion of "**SOP NO.:** BIO020.1" under the assessment of the Jeans (1999) study. The formulation sheet for "**BATCH NO.** *EF-005* ", containing laboratory rodent diet from "**LOT#:** *02/29/00* " in addition to "**STEAM ROLLED OATS**" obtained on "*03-08-00*" is consistent with preparation on 3/17/00 of a 9.994-kg amount of field rodent diet conforming to the relevant specifications in Protocol 1.216.

For the bioassay, a test group of 20 young adult deer mice (10 males, 10 females) and a similarly comprised control group were established. The mice were obtained on 4/20/00 from the Peromyscus Stock Center, University of South Carolina, Columbia, SC, and were reported to have been about 8-10 weeks old "at study initiation." The mice were housed in single-sex subgroups of 5 animals each "in suspended stainless steel caging." As with the Jeans (1999) study, reported cage dimensions were "16.0"L x 10"W x 7"H", making them 160 in^2 (1032 cm^2) in bottom area, just over half of 2.15 ft^2 (2000 cm^2) minimum size indicated in Protocol 1.216 when *Peromyscus* spp., are group-caged. The mice were kept under these conditions for a 3-day acclimation period, during which time they should have been fed a commercial mouse diet, prior to the start of the bait-exposure phase of the trial.

Males in the test group weighed 16.1-22.2 g (mean = 19.1 g) 3 days before the bait-exposure phase of the bioassay began. At the same time, test-group females averaged 17.6 g (range = 15.3-20.6 g); control-group males averaged 19.3 g (range = 16.8-22.6 g); and control-group females averaged 19.0 g (range = 16.8-22.7 g). The differences in mean weights between the sexes were 1.5 g in the test group and 0.3 g in the control group. Those figures are well below the 5-g maximum difference in mean weight between sexes that is stipulated in Protocol 1.216.

Test-group mice were to be offered a choice between the test bait and "EPA Field Rodent Challenge Diet for a 15-day period (5/15-30/00), after which time and surviving mice were to be maintained on challenge diet and observed for 5 more days or until they died, if sooner. Control-group mice were to be maintained on challenge diet for 20 straight days (5/15-6/3/00).

Feed was offered to mice in "jars", with 2 jars of toxic bait and 2 of field rodent challenge diet per cage. Procedures for jar deployments and rotations in this trial were like those discussed above for the Jeans (1999) trial. The 15-day bait-exposure period began on 5/15/00 and ran to 5/30/00. The 5-day post-exposure monitoring period, during which only challenge diet was offered, ran from 5/30/00 to 6/4/00. Control-group subjects were fed only the challenge diet for 20 days, having it in 4 jars/cage during the bait-exposure phase and in 2 jars/cage during the post-exposure monitoring period.

Results of this bioassay are summarized in Table 2. Test-group mortality was 90%, meeting the criterion of 90% for Protocol 1.216. Test-group victims died 3-10 days from the onset of bait exposure. The 2 survivors were males from the same subgroup.

All 8 test-group victims in the male subgroups lost weight (1.5-3.8 g) from 3 days prior to the start of the bait-exposure acclimation period until they expired. The 2 males that survived also lost weight, 1.8 and 1.9 g. Nine of the 10 victims in the female test group also reportedly lost weight (1.0-3.9 g) by their death dates, while one gained 1.1 g. Toxic symptoms reported for test-group animals included hind limb paralysis, lateral recumbency, rough hair coat, prone position, lethargy, tachypnea, prostration, red lacrimation, and ataxia. From lab notes appended to the report, it seems that the 2 survivors in male cage #2 appeared "*Normal*" throughout the trial. The symptoms reported for test-group victims are not inconsistent with anticoagulant poisoning. Necropsies were not reported.

All control-group subjects survived the 20 days from the start of the acclimation period to the end of the 5-day post-exposure monitoring period. Over that time span, all 10 control-group males lost weight (0.7-4.2 g). Something about the all-male communal caging situation and/or the field rodent diet apparently was not conducive to weight gain for these males. Three control-group females gained weight (0.8-1.6 g), 6 lost weight (0.1-1.5 g), and 1 maintained her initial weight. Despite the weight losses, all control-group mice were rated as "*Normal*" throughout the acclimation period and the subsequent 20 days.

Composite bait acceptance by the test-group was 47.9% (Table 2). Composite acceptance by females was greater than that by males. Male cage #2 was the only subgroup in which composite acceptance was below the 33% criterion indicated in Protocol 1.216 and was the lone subgroup with survivors. Those male survivors were the only live mice in their cage over the last 9 days of the bait-exposure period. During that time, 6.4 g of toxic bait consumption and 38.4 g of challenge diet consumption were recorded (14.3% acceptance).[3] Collectively, however, the cage #2 males were calculated to have consumed more of the bait than did the cage #1 males.

Control-group mice were calculated to have consumed 744.4 g of challenge diet during the 15-day bait-exposure phase of this trial and an additional 293.0 g during the 5-day post-exposure monitoring period for a grand total of 1037.4 g. Considering that 20 mice were in that group for 20, days (i.e., 400 mouse-days), mean daily consumption per "*Normal*" individual works out to 2.6 g/mouse/day.

Jeans (2000) reports that test-room temperatures were 20-26°C (68-~79°F) during the bioassay. That range in temperatures went a bit outside the range of 20-25°C (68-77°F) is specified in Protocol 1.216. Relative humidity in the test room reportedly was 45-78% and, therefore, strayed well beyond the range of 50-55% that is stipulated in Protocol 1.216. Without citing evidence regarding the effects of temperature or relative humidity on the performance of anticoagulant rodenticides, Jeans states that "these deviations should not affect the integrity of the study."

Except for the problems with controlling temperature and relative humidity in the test facility and the use of cages that were only about half the size specified in Protocol 1.216 if deer mice are group-caged, this efficacy trial appears to have been conducted competently. Results in the test group exceeded the criterion in Protocol 1.216 for bait acceptance (33%) and met the criterion for mortality (90%). The weight losses in all of the control-group males are of concern as they suggest that that housing situation was stressful to the animals. The study is accepted with reservations.

Labeling

The efficacy review package includes copies of proposed revised labeling, including a "**Pest Control Operator Use Label**", with separate labels for an "***OUTER CONTAINER – COMPLETE LABEL – PACKAGE WEIGHT 16 LB. OR GREATER***" and an "***INNER CONTAINER - COMPLETE LABEL – PACKAGE WEIGHT 2 LB. TO 10 LB.***", and an "**AGRICULTURAL USE LABEL**", with separate labels for an "***OUTER CONTAINER – COMPLETE LABEL – PACKAGE WEIGHT 8 LB, OR GREATER***" and an "***INNER CONTAINER – COMPLETE LABEL – PACKAGE WEIGHT 2 TO 4 LB.***". All 4 of these "***COMPLETE***" labels bear claims and "**DIRECTIONS FOR USE**" sections, among other required elements of labeling.

Within their "**DIRECTIONS FOR USE**" sections, the 2"***COMPLETE***" labels pertaining to "**Pest Control Operator Use**" include the sentence "Do not sell this product in individual containers holding less than 16 pounds of bait." For the "***COMPLETE***" labels pertaining to "**AGRICULTURAL USE**", the low-end limit on "individual containers" is "8 pounds of bait." Such lower limits were indicated in EPA's 2008 Risk Mitigation Decision for Ten Rodenticides (RMD, EPA, 2008). The "***INNER CONTAINER***" labels for package sizes smaller than these limits (i.e., 2- to 10-lb containers for the "**Pest Control Operator Use Label**" and 2- to 4-lb containers for the "**AGRICULTURAL USE LABEL**") bear the wording "**INDIVIDUAL SALE IS PROHIBITED BY LAW**". If individual containers included claims for controlling commensal rats but held less bait than is needed for a single rat-sized bait placement consistent with the "**DIRECTIONS FOR USE**" section of the accepted label, those containers could be considered to be misbranded under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). Such is not the case for 12455-79. The lower limits for container sizes for commensal rodenticide bait products that are not sold in or with bait stations are set forth only in the RMD rather than in FIFRA or the Code of Federal Regulations.

---

[3] As there were 2 mice alive, it is not clear how much of this reported bait consumption could be attributed to either one of them.

Changes to all 4 of these labels are proposed for amendments occasioned by the aforementioned "EPA/APSCRO agreement". Consequently, similar specific label comments are presented in more than one place in the "CONCLUSIONS" portion of this review, although I have attempted to limit the amount of such redundancy. More general label issues are addressed here. Label comments in this efficacy review, here and under "CONCLUSIONS", pertain only to claims of effectiveness and the "**DIRECTIONS FOR USE**" sections of the 4 labels.

Bell proposes front panel claims for all 4 labels that include "***KILLS RATS, MICE, AND VOLES***", "***KILLS WARFARIN RESISTANT NORWAY RATS***", and

> Rats, mice, and voles may consume a lethal dose in one night's feeding with first dead rodents appearing four of five days after feeding begins.

The first of these claims would replace "***KILLS RATS AND MICE***", which appears on the current accepted labeling for 12455-79 and on the labels of many other rodenticide baits that currently are claimed only to control commensal rodents (Norway rats, roof rats, and house mice, in the US). Adding "***VOLES***" (unqualified) to this claim is problematic because only one of the many types of voles that occur in the US is mentioned in the APSCRO letter.

The second of the front-panel claims quoted above, appropriately, is unchanged from the current label. No data have been submitted that support claims of effectiveness of Bromadiolone against Warfarin-resistant individuals of any species in the US other than the Norway rat.

The third proposed front-panel claim that is quoted above would expand the single-night's feeding claim from commensal rodents only to include all of the new targeted taxa that Bell proposes to claim. In order to support the single-night's feeding claim for commensal rodents, Bell (and others) had to submit efficacy data showing that Norway rats and house mice could be controlled to the criterion of 90% mortality in laboratory trials in which the bait-exposure period was limited to 24 hours (with challenge diet being offered simultaneously). Bell has not submitted such data for deer mice and has submitted no efficacy data at all for any of the other types of rodent that are proposed to be added as targeted pests to the label of 12455-79. The studies (Jeans, 1999, 2000) involving deer mice that were submitted included 15-day bait-exposure periods. There was substantial feeding on bait after the first 24 hours (e.g., 104.3 g – 79% of all toxic bait consumption -- in the Jeans, 2000, study) and neither trial produced 100% mortality in the test group.

CONCLUSIONS

1. The laboratory efficacy report by Jeans (1999) has been assigned the MRID Number 495528-01. In that study, deer mice accepted the test material (Batch No. "03241") at 37.7% of total calculated dietary intake; and 19 (95%) of the animals in the test group died. Those results exceed the applicable criteria of 33% acceptance and 90% mortality set forth in Protocol 1.216. This study applies to the formulation used as the test material, which was consistent in composition with the bait described by the current Confidential Statement of Formula (CSF), dated October 24, 2013, for this product (see CONFIDENTIAL ATTACHMENT).

   The Jeans (1999) study is accepted with reservations due use of cages that were too small and to fluctuations of relative humidity and temperature in the test room that went well beyond the ranges set forth in Protocols 1.216.

2. The laboratory efficacy report by Jeans (2000) has been assigned the MRID Number 495528-02. In that study, deer mice accepted the test material (Batch No. "68061") at 47.9% of total calculated dietary intake; and 18 (90%) of the animals in the test group died. Those results exceed the criterion of 33% acceptance and meet the criterion of 90% mortality set forth in Protocol 1.216. This study applies to the formulation used as the test material, which was consistent in composition with the bait described on the current Confidential Statement of Formula (CSF), dated October 24, 2013, for this product (see CONFIDENTIAL ATTACHMENT).

The Jeans (1999) study is accepted with reservations due use of cages that were too small and to fluctuations of relative humidity and temperature in the test room that went well beyond the ranges set forth in Protocols 1.216. Together, the Jeans (1999) and Jeans (2000) studies support claims for controlling deer mice with this product as is currently is made.

3. Documents obtained from Bell Laboratories, Inc., during the conduct of this review indicate that the current CSF for this product is consistent with the composition of this product as it was mixed for the batches used in the efficacy trials involving deer mice (and apparently how it is made for the commercial market). However, the current CSF is not accurate regarding how the various substances that comprise this product come to be in it. If, for example, two or more components are obtained from another entity already mixed together as one product, the CSF must identify the product that is obtained and added to the formulation rather than to list its components separately. If several components are purchased separately and combined as a premix at the bait production facility, those components would be listed separately on the CSF; but the manufacturing process that is reported to EPA would have to discuss the creation and composition of the premix. Some components of purchased mixtures should be identified on the CSF, under the name of the purchased mixture. That would be required for the active ingredient if it were obtained as a concentrate. For rodenticide baits, the concentration of a dye and/or a bittering agent within a purchased product used in formulation should be identified on the CSF as such components can affect the palatability of baits.

4. On the first panels of all four label components ("***OUTER CONTAINER – COMPLETE LABEL – PACKAGE WEIGHT 16 LB. OR GREATER***" and "***INNER CONTAINER - COMPLETE LABEL – PACKAGE WEIGHT 2 LB. TO 10 LB.***" for pest control operator use and "***OUTER CONTAINER – COMPLETE LABEL – PACKAGE WEIGHT 8 LB, OR GREATER***" and "***INNER CONTAINER – COMPLETE LABEL – PACKAGE WEIGHT 2 TO 4 LB.***" for agricultural use), replace the proposed claim "***KILLS RATS, MICE, AND VOLES***" with either "***KILLS RATS AND MICE***" or "***KILLS RATS, MICE, AND MEADOW VOLES***".

5. On all 4 label components, change the proposed claim

> Rats, mice, and voles may consume a lethal dose in one night's feeding with first dead rodents appearing four of five days after feeding begins.

back to

> Norway rats, roof rats, and mice may consume a lethal dose in one night's feeding with first dead rodents appearing four of five days after feeding begins.

No efficacy data relevant to a "single night's feeding" claim have been submitted for any of the types of rodents for which control claims are newly proposed. The only efficacy data that were submitted relevant to any of the proposed new claims were laboratory efficacy trials with deer mice in which the bait-exposure period lasted 15 days rather than just 24 hours. Mortality results in those trials were 90% and 95%, and most of the calculated consumption of the toxic bait occurred after the first 24 hours of exposure.

6. In the first sentence of the first "**USE RESTRICTIONS**:" paragraph in the "**DIRECTIONS FOR USE**" section on the "***OUTER CONTAINER – COMPLETE LABEL – PACKAGE WEIGHT 16 LB. OR GREATER***" and "***INNER CONTAINER - COMPLETE LABEL – PACKAGE WEIGHT 2 LB. TO 10 LB.***" for pest control operator use, identify the species of woodrats (*Neotoma*) for which control is to be claimed. Do not include any threatened or endangered species or subspecies of woodrats in this list. Limit the claim for "Cotton rats" to *Sigmodon hispidus*.

In the third sentence of this same paragraph, change "port of terminal" to "port or terminal".

7. In the first sentence of the "**SELECTION OF TREATMENT AREAS:**" paragraph in the "**DIRECTIONS FOR USE**" section on the "***OUTER CONTAINER – COMPLETE LABEL – PACKAGE WEIGHT 16 LB. OR GREATER***" and "***INNER CONTAINER - COMPLETE LABEL – PACKAGE WEIGHT 2 LB. TO 10 LB.***" for pest control operator use, change "voles" to "meadow voles".

   In the second sentence of the same paragraph, replace "rats, mice, voles, or their signs" with "signs of rats, mice, or meadow voles".

8. In the second sentence of the "**RATS:**" paragraph under "**APPLICATION DIRECTIONS:**" in the "**DIRECTIONS FOR USE**" section on the "***OUTER CONTAINER – COMPLETE LABEL – PACKAGE WEIGHT 16 LB. OR GREATER***" and "***INNER CONTAINER - COMPLETE LABEL – PACKAGE WEIGHT 2 LB. TO 10 LB.***" for pest control operator use, replace "signs of rat activity cease" with "there no longer are fresh signs of rat activity."

9. In the proposed "**MICE AND VOLES:**" paragraph under "**APPLICATION DIRECTIONS:**" in the "**DIRECTIONS FOR USE**" section on the "***OUTER CONTAINER – COMPLETE LABEL – PACKAGE WEIGHT 16 LB. OR GREATER***" and "***INNER CONTAINER - COMPLETE LABEL – PACKAGE WEIGHT 2 LB. TO 10 LB.***" for pest control operator use, change the paragraph heading to "**MICE AND MEADOW VOLES**".

   In the second sentence of the same paragraph, change "8 to 12 foot intervals" to "8- to 12-foot intervals" (or to "intervals of 8 to 12 feet").

   In the fourth sentence of the same paragraph, replace "signs of mouse activity cease" with "there no longer are fresh signs of mouse or meadow vole activity."

10. In the third sentence of the "**FOLLOW-UP:**" paragraph under "**APPLICATION DIRECTIONS:**" in the "**DIRECTIONS FOR USE**" section on the "***OUTER CONTAINER – COMPLETE LABEL – PACKAGE WEIGHT 16 LB. OR GREATER***" and "***INNER CONTAINER - COMPLETE LABEL – PACKAGE WEIGHT 2 LB. TO 10 LB.***" for pest control operator use, replace "prevent" with "discourage".

    In the last sentence of the same paragraph, insert "them" between "replenish" and "as".

11. In the first sentence of the first "**USE RESTRICTIONS:**" paragraph in the "**DIRECTIONS FOR USE**" section on the "***OUTER CONTAINER – COMPLETE LABEL – PACKAGE WEIGHT 8 LB. OR GREATER***" and "***INNER CONTAINER - COMPLETE LABEL – PACKAGE WEIGHT 2 TO 4 LB.***" for agricultural use, identify the species of woodrats (*Neotoma*) for which control is to be claimed. Do not include any threatened or endangered species or subspecies of woodrats in this list. Limit the claim for "Cotton rats" to *Sigmodon hispidus*.

12. In the first sentence of the "**SELECTION OF TREATMENT AREAS:**" paragraph in the "**DIRECTIONS FOR USE**" section on the "***OUTER CONTAINER – COMPLETE LABEL – PACKAGE WEIGHT 8 LB. OR GREATER***" and "***INNER CONTAINER - COMPLETE LABEL – PACKAGE WEIGHT 2 TO 4 LB.***" for agricultural use, change "voles" to "meadow voles".

    In the second sentence of the same paragraph, replace "rats, mice, voles, or their signs" with "signs of rats, mice, or meadow voles".

13. In the second sentence of the "**RATS:**" paragraph under "**APPLICATION DIRECTIONS:**" in the "**DIRECTIONS FOR USE**" section on the "***OUTER CONTAINER – COMPLETE LABEL – PACKAGE WEIGHT 8 LB. OR GREATER***" and "***INNER CONTAINER - COMPLETE LABEL – PACKAGE WEIGHT 2 TO 4 LB.***" for agricultural use, replace "signs of rat activity cease" with "there no longer are fresh signs of rat activity."

14. In the proposed "**MICE AND VOLES:**" paragraph under "**APPLICATION DIRECTIONS:**" in the "**DIRECTIONS FOR USE**" section on the "***OUTER CONTAINER – COMPLETE LABEL – PACKAGE WEIGHT 8 LB. OR GREATER***" and "***INNER CONTAINER - COMPLETE LABEL – PACKAGE WEIGHT 2 LB. TO 10 LB.***" for agricultural use, change the paragraph heading to "**MICE AND MEADOW VOLES**".

    In the second sentence of the same paragraph, change "8 to 12 foot intervals" to "8- to 12-foot intervals" (or to "intervals of 8 to 12 feet").

    In the fourth sentence of the same paragraph, replace "signs of mouse activity cease" with "there no longer are fresh signs of mouse or meadow vole activity."

15. In the third sentence of the "**FOLLOW-UP:**" paragraph under "**APPLICATION DIRECTIONS:**" in the "**DIRECTIONS FOR USE**" section on the "***OUTER CONTAINER – COMPLETE LABEL – PACKAGE WEIGHT 8 LB. OR GREATER***" and "***INNER CONTAINER - COMPLETE LABEL – PACKAGE WEIGHT 2 LB. TO 10 LB.***" for agricultural use, replace "prevent" with "discourage".

    In the last sentence of the same paragraph, insert "them" between "replenish" and "as".

Reference

EPA. 2008. Risk mitigation decision for ten rodenticides. Office of Pesticide Programs, Office of Prevention, Pesticides, and Toxic Substances, U.S., Environmental Protection Agency, Washington, DC, May 28, 2008, 37 pp. plus appendices.

Table 1. Test-group results in "15-day" choice test involving Bromadiolone All-Weather Blox and deer mice deer mice (Jeans, 1999; MRID# 495528-01).

Study Number	Cage Number	Sex	Number of Subjects	Bait Consumed (g)	Challenge Diet Consumed (g)	Percent Bait Acceptance	Mortality	Days to Death
BEL.0999/	1	M	5	16.6	53.1	23.8%	5	3-9
BE430	2	M	5	38.1	44.3	46.2%	5	5-14
Subtotals		Males	10	54.7	97.4	36.0%	10	3-14
BEL/0999/	1	F	5	33.1	66.7	33.2%	4	5-9
BE430	2	F	5	34.6	37.9	47.7%	5	4-8
Subtotals		Females	10	67.7	104.6	39.3%	9	5-9
Totals	All	Both	20	122.4	202.0	37.7%	19	3-14
Mean						36.8%	95%	

Table 2. Test-group results in "15-day" choice test involving Bromadiolone All-Weather Blox and deer mice deer mice (Jeans, 2000; MRID# 495528-02).

Study Number	Cage Number	Sex	Number of Subjects	Bait Consumed (g)	Challenge Diet Consumed (g)	Percent Bait Acceptance	Mortality	Days to Death
BEL.0500/	1	M	5	26.0	32.4	44.5%	5	3-8
BE462	2	M	5	27.3	72.8	27.3%	3	4-6
Subtotals		Males	10	53.3	105.2	33.6%	8	3-8
BEL/0500/	1	F	5	38.7	19.2	66.8%	5	5-10
BE462	2	F	5	40.7	20.2	66.8%	5	3-8
Subtotals		Females	10	79.4	39.4	66.8%	10	3-10
Totals	All	Both	20	132.7	144.6	47.9%	18	3-10
Mean						40.7%	90%	

Inert ingredient information may be entitled to confidential treatment

Inert ingredient information may be entitled to confidential treatment

Inert ingredient information may be entitled to confidential treatment